Acute hypertension impairs endothelium-dependent vasodilatation

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In a recent paper in Clinical Science, Millgård and Lind [1] reported experiments investigating the possibility that acute hypertension impairs endothelium-dependent vasodilatation in normotensive subjects. Their major finding was that systemic (intravenous) infusion of noradrenaline, sufficient to raise mean arterial blood pressure from $83 \pm 6$ to $116 \pm 10$ mmHg, significantly reduced the increase in forearm blood flow seen in response to brachial arterial infusion of methacholine, but not that to sodium nitroprusside. In contrast, local intra-arterial infusion of noradrenaline (which had no systemic effects) inhibited the vasodilator effects of methacholine and sodium nitroprusside to similar extents. Millgård and Lind [1] concluded that the acute hypertension induced by noradrenaline caused a selective inhibition of endothelium-mediated vasodilator function, but pointed out in their Discussion that the results were not unequivocal proof of an effect of a rise in arterial blood pressure on nitric oxide production.

We would like to propose an alternative explanation for the findings of Millgård and Lind [1], which involves a mechanism not considered by them. From their data, the intravenous infusion of noradrenaline raised mean arterial blood pressure (from 83 to 116 mmHg) and total peripheral resistance index (from 1765 ± 319 to $2373 \pm 554$ dyn \( \times \) s \( \times \) m\(^2\)/cm\(^5\)), without affecting heart rate ($69 \pm 8$ and $56 \pm 11$ beats/min) or cardiac index ($3.7 \pm 0.6$ and $4.0 \pm 0.8$ l/min\(^{-1}\) m\(^{-2}\)). Given the well-known, potent positive chronotropic and inotropic effects of noradrenaline, the most likely explanation of the apparent absence of such effects here is that its hypertensive action caused reflex vagal activation and withdrawal of sympathetic tone, sufficient to offset its direct cardiac actions.

The rise in arterial blood pressure, then, was entirely attributable to the rise in total peripheral resistance, but it is notable that this did not involve the forearm vascular bed since, during noradrenaline infusion, forearm blood flow rose (from $4.2 \pm 1.2$ to $5.7 \pm 1.4$ ml/min\(^{-1}\) 100 ml\(^{-1}\) tissue) and forearm vascular resistance did not change (as calculated from forearm blood flow and mean arterial blood pressure). The apparent lack of effect of systemic infusion of noradrenaline in the forearm contrasts with its potent vasoconstrictor action when given into the brachial artery (50% increase in forearm vascular resistance). The most likely explanation of the absence of a forearm vasoconstrictor effect of intravenous noradrenaline is a balance between the opposing vasodilator influence of reflex withdrawal of forearm sympathetic tone in response to the hypertension, and the vasoconstrictor action of exogenous noradrenaline. This seems reasonable, given what happened in the heart (see above).

If these arguments are accepted, then, in the experiments of Millgård and Lind [1], in the baseline condition, forearm sympathetic vasoconstrictor tone would be present, but during systemic infusion of noradrenaline it would be absent (or much reduced). Since there are muscarinic receptors on noradrenergic nerve terminals which, when activated, inhibit the release of noradrenaline [2], it is feasible that a component of the forearm vasodilator effect of methacholine is due to such prejunctional inhibition. It is this component which would be diminished when sympathetic tone was reduced by acute hypertension, thereby explaining the apparently selective inhibition of methacholine-induced forearm vasodilatation with systemic noradrenaline infusion. The lack of such an effect with brachial arterial infusion of noradrenaline is consistent with this proposal, since this intervention had no systemic effects, and hence would not have caused reflex inhibition of forearm sympathetic tone.

In a study dealing with the forearm vasodilator effects of acetylcholine and methacholine, Chowienczyk et al. [3] cited work [4,5] which appeared to exclude the possibility that inhibition of noradrenaline release was a significant component of the vasodilatation. In reaching this conclusion the studies of Linder et al. [4] and Creager et al. [5] relied upon the observation that the forearm vasodilator responses to the muscarinic agonists were not inhibited by phentolamine. However, neither study demonstrated an impairment of sympathetic vasomotor tone in the presence of phentolamine, or, more importantly, examined the possibility of enhanced vasodilator responses to acetylcholine or methacholine in the presence of increased sympathetic vasomotor tone in the forearm. If our hypothesis is tenable, it indicates that experimental manipulation of forearm sympathetic tone should have predictable effects on the vasodilator action of methacholine; we would be very interested to see the results of such experiments.
If systematic experimental investigations reveal that a significant component of the forearm vasodilator response to methacholine (or acetylcholine) is due to prejunctional inhibition of noradrenaline release, then all those studies which have used this intervention as a means of assessing endothelium-dependent vasodilatation need to be looked at afresh.

REFERENCES


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